REMARKS/ARGUMENTS

Claims 6-23 are active. New Claims 6-23 find support in the original claims and specification as follows: Claims 6-14 (Claims 1-5, pages 1-2), Claim 15 (page 3, line 7), Claims 16-17 (page 5, line 2), and Claims 18-20 (page 2, line 29 *ff.*) and Claims 21-23 (page 3, lines 8-15).

Original Claim 5 refers to a "cyclohexyl group" as does page 6, lines 12-13 of the specification which describe this compound by reference to Example 23 of EP-A-0 630 376 (on page 15, line 30). The compound in Example 23 of EP '376 is, in fact, "cyclohexylmethyl". Moreover, page 1 of the specification generally discloses compounds of formula (I) by reference to EP '376 and uses nonlimiting language with regard to the R group (specification, page 1, line 9). Thus, new Claims 6 and 13 refer to "cyclohexylmethyl"—the correct compound of Example 23 of EP '376. Accordingly, the Applicants do not believe that any new matter has been added. Favorable consideration of these amendments and allowance of this application is now respectfully requested.

Rejection—35 U.S.C. §112, second paragraph

Claim 5 was rejected under 35 U.S.C. 112, second paragraph, for lack of antecedent basis. This rejection is now moot.

Rejection—35 U.S.C. §103

Claims 1-4 were rejected under 35 U.S.C. 103(a) as being unpatentable over Gaster et al., EP 0630376[1], in view of Smith et al., Neurosci. Lett. 271:61 and Jorum et al., Pain 101:229. This rejection would not apply to the new claims because the prior art does not disclose or suggest that a compound of formula (I) can treat neuropathic pain. Neuropathic

[1] Cited as EP 0630736 in the Official Action.

pain, as explained in more detail below is distinct from pain associated with other diseases, and denotes a pain initiated or caused by a primary lesion or dysfunction in the nervous system.

Gaster [0050] only describes treatment of irritable bowel syndrome, gastro-oesophagal reflux disease, dyspepsia, atrial arrhythmias and stroke, anxiety and/or migraine with compounds of formula (I) and does not disclose or suggest use of these compounds for treating neuropathic pain.

Smith and Jorum do not disclose the compounds of formula (I) and thus, provide no motivation or suggestion to use compounds of formula (I) to treat any disease, or specifically neuropathic pain. Thus, none of the cited prior art provides any explicit motivation for using a compound of formula (I) to treat neuropathic pain.

The rejection is based on the following premises:

(A) That 5HT4 receptor antagonists (like the compounds of formula I and SB 207266 of Smith) can be used to treat any type of allodynia.

(B) That Jorum relate allodynia and hyperalgesia to neuropathic pain.

Thus, according to the Official Action, it would have been obvious to use a 5HT4 receptor antagonist to treat allodynia, and since allodynia is associated with neuropathic pain, such a treatment would also ameliorate neuropathic pain.

However, this argument must fail because these premises are incorrect.

With regard to (A), Smith only describes treatment of intestinal allodynia and says nothing about neurological allodynia. Moreover, Smith only indicates that 5HT4 receptor antagonists potentiate inhibition of intestinal allodynia by 5HT3 receptor antagonist (see summary, line 3, as well as page 61, right column, line 7 to 9; and Fig. 1 on page 62). Smith merely suggests that "$5HT_4$ receptor activation enhances the ability of $5HT_3$ receptor activation to induce intestinal allodynia" (see summary, last two lines). It is silent about the

effects of administering a 5-HT4 antagonist. Thus, the rejection has provided no nexus between the administration of a 5HT4 receptor antagonist *per se* (or specifically a compound of formula I) and treatment of allodynia of any type. Similarly, there is no evidence of record that allodynia associated with neuropathic pain is related at all to allodynia in the intestines. Significantly, the test used by Smith does not involve any primary lesion or dysfunction in the nervous system. Therefore, the experimental data disclosed by Smith can not be correlated with neuropathic pain in any way. Indeed, in the absence of a primary lesion or dysfunction in the nervous system a pain cannot be defined as neuropathic in nature (see the above definition).

Furthermore, the Office has not explained why a compound of formula I would exhibit similar properties to the structurally distinct SB-207266 compound of Smith. Smith provides no evidence that other 5HT4 antagonists like the compound of formula I would have any effect on intestinal allodynia, and no suggestion at all that such antagonist would have any effect on allodynia associated with neuropathic pain.

Jorum disclose that Alfentanil significantly reduced cold allodynia (see summary, line 10). However, this reference is silent about the action of Alfentanil on neuoropathic pain. Moreover, Alfentanil is μ-opioid agonist, not a 5-HT_4 receptor antagonist. Thus, Jorum is non-analogous art because it discloses a different class of drugs, does not disclose compounds of formula I, and discloses nothing about the effects of drugs on neuropathic pain, as opposed to allodynia associated with cold.

The rejection indicates:

> Smith et al teaches that 5-HT4 receptor antagonist such as SB 207266 shows an anti-allodynic activity and Jorum et al teaches that allodynia and hyperalgesia are frequent clinical findings in patient with neuropathic path. Hence inhibiting allodynia in patients provides a method of treating a neuropathic pain.

However, this reasoning is a mere hindsight reconstruction attempt which involves a number of mistakes. Specifically, the Office attempts to correlate 5-HT4 receptor antagonist to neuropathic pain via allodynia. However, the argument that Smith et al. teaches that a 5-HT_4 receptor antagonist such as SB 207266 shows an anti-allodynic activity is incorrect. Indeed, SB 207266 does not show any anti-allodynic activity in the test performed by Smith et al. unless it is associated with a 5-HT_3 receptor antagonist. Thus, Smith et al. would be a proper reference only if the present invention was addressed to an association of both a 5-HT_3 and p 5-HT_4 antagonist. Moreover, the test used by Smith et al. does not involve any primary lesion or dysfunction in the nervous system. Therefore, the experimental data disclosed by Smith et al. can not be correlated with neuropathic pain in any way. Indeed, in the absence of a primary lesion or dysfunction in the nervous system a pain cannot be defined as neuropathic in nature (see IASP definition below).

The addition of Jorum et al. does not remedy this deficiency. While the Examiner is correct when he states that Jorum et al. teaches that allodynia and hyperalgesia are frequent clinical findings in patient with neuropathic pain, he is wrong when he speculates that inhibiting allodynia in patients would provide a method of treating a neuropathic pain. Particularly, Jorum et al. is completely silent about the action of Alfentanil on neuoropathic pain. There is no basis at all in Smith et al. to infer that SB 207266 shows an anti-allodynic activity in the absence of a 5-HT_3 receptor antagonist, and no basis in Jorum et al. to infer that inhibiting allodynia in patients would provide a method of treating a neuropathic pain.

The Applicants provide the following technical definitions in further support of the arguments above. According to IASP (International Association for the Study of Pain) the following terms are defined as follows:

Neuropathic Pain: this term denotes a pain initiated or caused by a primary lesion or dysfunction in the nervous system.

Note: See also Neurogenic Pain and Central Pain. Peripheral neuropathic pain occurs when the lesion or dysfunction affects the peripheral nervous system. Central pain may be retained as the term when the lesion or dysfunction affects the central nervous system.

Allodynia: this term denotes a pain due to a stimulus which does not normally provoke pain.

Note: The term allodynia was originally introduced to separate from hyperalgesia and hyperesthesia, the conditions seen in patients with lesions of the nervous system where touch, light pressure, or moderate cold or warmth evoke pain when applied to apparently normal skin. Allo means "other' in Greek and is a common prefix for medical conditions that diverge from the expected. Odynia is derived from the Greek word "odune" or "odyne," which is used in "pleurodynia" and "coccydynia" and is similar in meaning to the root from which we derive words with -algia or -algesia in them. Allodynia was suggested following discussions with Professor Paul Potter of the Department of the History of Medicine and Science at The University of Western Ontario.

The words "to normal skin" were used in the original definition but later were omitted in order to remove any suggestion that allodynia applied only to referred pain. Originally, , the pain-provoking stimulus was described as 'non-noxious." However, a stimulus may be noxious at some times and not at others, for example, with intact skin and sunburned skin, and also, the boundaries of noxious stimulation may be hard to delimit. Since the Committee aimed at providing terms for clinical use, it did not wish to define them by reference to the specific physical characteristics of the stimulation, e.g., pressure in kilopascals per square centimeter. Moreover, even in intact skin there is little evidence one way or the other that a strong painful pinch to a normal person does or does not damage tissue. Accordingly, it was considered to be preferable to define allodynia in terms of the response to clinical stimuli and

to point out that the normal response to the stimulus could almost always be tested elsewhere in the body, usually in a corresponding part.

Further, allodynia is taken to apply to conditions which may give rise to sensitization of the skin, e.g. sunburn inflammation, trauma.

It is important to recognize that **allodynia** involves a change in the quality of a sensation, whether tactile, thermal, or of any other sort. The original modality is normally non-painful, but the response is painful. There is thus a loss of specificity of a sensory modality.

By contrast, **hyperalgesia** (q.v.) represents an augmented response in a specific mode, viz., pain. With other cutaneous modalities, hyperesthesia is the term which corresponds to hyperalgesia, and as with hyperalgesia, the quality is not altered. In allodynia the stimulus mode and the response mode differ, unlike the situation with hyperalgesia. This distinction should not be confused by the fact that allodynia and hyperalgesia can be plotted with overlap along the same continuum of physical intensity in certain circumstances, for example, with pressure or temperature.

Hyperalgesia: this term denotes an increased response to a stimulus which is normally painful.

Note: Hyperalgesia reflects increased pain on suprathreshold stimulation. For pain evoked by stimuli that usually are not painful, the term allodynia is preferred, while hyperalgesia is more appropriately used for cases with an increased response at a normal threshold, or at an increased threshold, e.g.. in patients with neuropathy. It should also be recognized that with allodynia the stimulus and the response are in different modes, whereas with hyperalgesia they are in the same mode. Current evidence suggests that hyperalgesia is a consequence of perturbation of the nociceptive system with peripheral or central sensitization, or both, but it is important to distinguish between the clinical phenomena,

which this definition emphasizes, and the interpretation, which may well change as knowledge advances.

For the reasons set forth above, the Applicants respectfully request that this rejection be withdrawn.

Rejection—35 U.S.C. §103

Claims 1-4 were rejected under 35 U.S.C. 103(a) as being unpatentable over Gaster et al., EP 0630736, in further in view of Burnstein et al., Brain 123:1703 and Jorum et al., Pain 101:229. Gaster and Jorum have been addressed above. Neither discloses or suggests using a compound of formula (I) to treat neuropathic pain. Only Gaster even describes a compound of formula (I) and Jorum is directed to treatments using a different class of drugs: μ-opioid agonists, not 5-HT_4 receptor antagonists.

Burnstein describe the development of cutaneous allodynia during a migraine attack. However, nothing in this reference teaches or suggests that any class of drugs capable of treating cutaneous allodynia will successfully treat migraine, or more importantly, neuropathic pain.

Significantly, there is no link whatsoever between migraine (which is thought to arise from chemical activation of sensory nerves that supply intracranial blood vessels and meninges, see the first six lines of Burnstein) and neuropathic pain which, in contrast, is caused by a primary lesion or dysfunction in the nervous system. Thus, there cannot be any reasonable expectation of success for treating neuropathic pain using a compound that treats cutaneous allodynia or even migraine.

Moreover, to link migraine to neuropathic pain via allodynia, Burstein should teach that a fully developed migraine attack benefits from a possible drug capable of treating

cutaneous allodynia. In contrast, Bernstein is completely silent about the effects on migraine of drugs capable of treating cutaneous allodynia.

In turn, Jorum does not establish a link between the treatment of allodynia and the treatment of neuropathic pain. Indeed, Jorum et al. teaches that Alfentanil is useful to treat allodynia only. However, it is completely silent about the action of Alfentanil on the neuoropathic pain. Thus, there is no suggestion or reasonable expectation of success in Gaster, Burstein or Jorum that inhibiting allodynia would provide a method of treating a neuropathic pain. Accordingly, the Applicants respectfully request that this rejection be withdrawn as none of the cited prior art suggests or provide a reasonable expectation of success for use of a compound of formula I to treat neuropathic pain.

Conclusion

In view of the amendments and remarks above, the Applicants respectfully submit that this application is now in condition for allowance. Early notice of such is earnestly requested.

Respectfully submitted,

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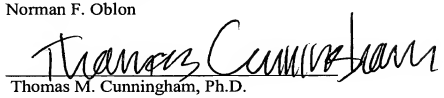

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